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CLINICAL REPORT

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A *de novo CSDE1* variant causing neurodevelopmental delay, intellectual disability, neurologic and psychiatric symptoms in a child of consanguineous parents

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Abstract

CSDE1 encodes the cytoplasmic cold shock domain-containing protein E1 (CSDE1), which is highly conserved across species and functions as an RNA-binding protein involved in translationally coupled mRNA turnover. CSDE1 displays a bidirectional role: promoting and repressing the translation of RNAs but also increasing and decreasing the abundance of RNAs. Preclinical studies highlighted an involvement of *CSDE1* in different forms of cancer. Moreover, *CSDE1* is highly expressed in human embryonic stem cells and plays a role in neuronal migration and differentiation. A genome-wide association study suggested *CSDE1* as a potential autism-spectrum disorder risk gene. A multicenter next generation sequencing approach unraveled likely causative heterozygous variants in *CSDE1* in 18 patients, identifying a new autism spectrum disorder-related syndrome consisting of autism, intellectual disability, and neurodevelopmental delay. Since then, no further patients with *CSDE1* variants have been reported in the literature. Here, we report a 9.5-year-old girl from a consanguineous family of Turkish origin suffering from profound delayed speech and motor development, moderate intellectual disability, neurologic and psychiatric symptoms

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as well as hypoplasia of corpus callosum and mildly reduced brain volume on brain magnetic resonance imaging associated with a recurrent *de novo* mutation in *CSDE1* (c.367C > T; p.R123*) expanding the phenotypical spectrum associated with pathogenic *CSDE1* variants.

KEYWORDS
anxiety, developmental delay, intellectual disability, muscle weakness, pathological laughter and cry

1 | INTRODUCTION

CSDE1 encodes the cytoplasmic cold shock domain-containing protein E1 (CSDE1), which is highly conserved across species (Guo et al., 2019). CSDE1 functions as an RNA-binding protein involved in translationally coupled mRNA turnover (Chang et al., 2004) and is required for efficient formation of stress granules (Youn et al., 2018). Interestingly, CSDE1 displays a bidirectional role: promoting and repressing the translation of RNAs but also increasing and decreasing the abundance of RNAs (Guo et al., 2020; Kakumani et al., 2020). Ju Lee and co-workers demonstrated that *CSDE1* is highly expressed in human embryonic stem cells (hESCs) and post-transcriptionally modulates core components of multiple regulatory nodes of hESC identity and neurogenesis (Ju Lee et al., 2017). Hence, *CSDE1* has been implicated in both neuronal migration and differentiation (Ju Lee et al., 2017; Kobayashi et al., 2013) and a genome-wide association study suggested *CSDE1* as a potential autism-spectrum disorder (ASD) risk gene (Xia et al., 2014). Indeed, a multicenter next generation sequencing (NGS) approach unraveled likely causative heterozygous variants in *CSDE1* in 18 patients, identifying a new ASD-related syndrome (Guo et al., 2019). The most consistent phenotypes include a combination of ASD, intellectual disability, delayed speech, and delayed motor development. Half of the patients reported in this study presented with varied abnormalities on brain magnetic resonance imaging (MRI), for example, thin or short corpus callosum, white matter alterations with resulting prominent ventricular system, thickened cortex, and mild cerebellar vermis hypoplasia. Along this line, *in vitro* and *in vivo* functional analyses highlight the important role of Csde1 in neuronal development and synaptic transmission (Guo et al., 2019).

Here, we report on a girl born to consanguineous parents of Turkish origin suffering from delayed speech and motor development, moderate intellectual disability, neurologic symptoms, psychiatric symptoms and hypoplasia of corpus callosum and mildly reduced brain volume on brain MRI associated with a *de novo* mutation in the *CSDE1* gene (c.367C > T; p.R123*, ENST00000369530) already reported three times in the literature as pathogenic (Guo et al., 2019). However, although this variant seems to be the most recurrent pathogenic dominant variant in *CSDE1* identified thus far, muscle weakness, as present in our patient, has not been linked to the phenotypical spectrum of this disease before.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

Written informed consent for all diagnostic steps as well as the permission to publish clinical data and photographs were obtained from both parents and the ethics committee of University Medicine Essen (19-9011-BO, February 4, 2020) had granted ethical approval. The study was conducted in accordance with the principles of the Declaration of Helsinki of 1975, as revised in 1983.

2.2 | Genetic analyses

In the genetic work-up, first regular karyotyping was performed followed by array-based comparative genomic hybridization (CGH). Under the suspicion of an autosomal recessive disorder, a trio exome sequencing was carried out. Whole exome sequencing (WES) was performed by the Genomics Platform at the Broad Institute of MIT and Harvard, Cambridge, USA. Libraries were created with an Illumina exome capture (38 Mb target) and sequenced with a mean target coverage of >80x. Exome sequencing data were processed and analyzed on the RD-Connect Genome-Phenome Analysis Platform (https://platform.rdconnect.eu/genomics). Likely pathogenic variants were identified applying standard filtering criteria: minor allele frequency <1% and high-to-moderate variant effect predictor. Shortlisted variants were interrogated for their predicted in silico deleteriousness and previous known association with human disease.

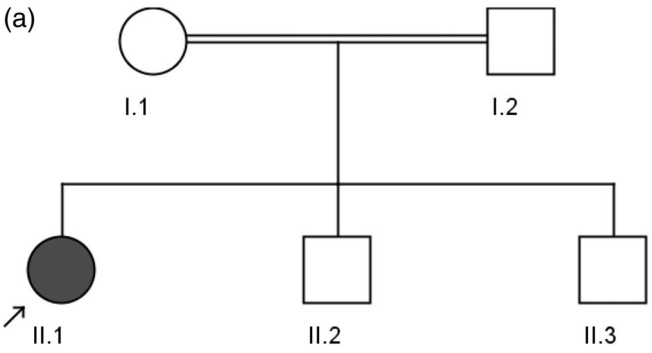
3 | CLINICAL REPORT

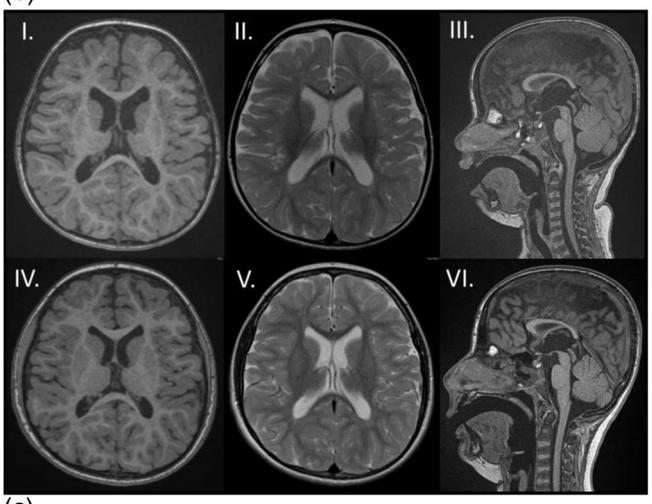
The female patient is the third child of healthy, consanguineous parents (cousins I°) of Turkish origin. Family history is unremarkable (the 16- and 19-year-old brothers showed normal development) (see Figure 1a). Parental age at conception was 34 (father) and 32 (mother). Pregnancy was uneventful with unremarkable findings on prenatal ultrasound screening and the mother reported normal fetal movements.

3.1 | 0–4 weeks (newborn)

Spontaneous delivery was at term (38 weeks of pregnancy) with normal birth measurements (weight: 3790 g [93. percentile, 1.45z],

length: 50 cm [43. percentile, −0.17z], head circumference: 35 cm [71. percentile, 0.54z]) (percentiles from: Voigt et al., 2006) and Apgar 1′ 9, 5′ 10, 10′ 10. Due to mild hyperbilirubinemia, phototherapy was performed on fifth day of life.





3.2 | 1–12 months of age (infant)

The patient was breastfed for 6 months and thrived well. At preventive medical check-ups with 4 weeks, 3 and 6 months, no abnormalities were recorded by the pediatrician. At the age of 12 months, it was noted that she was neither able to crawl coordinated nor to sit without help and did not try to pull herself up.

3.3 | 1–2 years of age (toddler)

The patient was presented at our department for the first time at the age of 24 months due to the above-mentioned neurodevelopmental delay. Motor milestones were significantly delayed: she learned to sit without assistance at the age of 14 months and was able to move around by sliding on her bottom and walking along furniture by 23 months. These milestones were achieved with the help of the early support ("Frühförderung") she received from the age of 21 months. At the age of 24 months, she was still not able to pull herself up. Besides gross motor delay, fine motor abilities were also delayed, not being able to complete simple puzzles at the age of 24 months. The patient was raised bilingual (Turkish/German) and was only able to speak eight Turkish words (no two-word-sentences) at the age of 24 months. Additionally, parents reported problems chewing and swallowing small pieces of food, porridge was still preferred. Due to the neurodevelopmental delay, basic diagnostic work-up was performed at the age of 2 years and 7 months: brain MRI (Figure 1b I–III) showed mildly reduced brain volume with moderate dilation of the ventricular system, slight enlargement of prefrontal subarachnoid space, slim white matter, and a thin and short corpus callosum with a partial lack of the splenium. However, myelination and gyration were adequately developed for the child's age. Chromosome analysis revealed a normal female karyotype (46, XX), ultrasound of the abdomen, echocardiography, electroencephalography, standard laboratory

FIGURE 1 (a) Family Pedigree: I.1 and I.2: Healthy, consanguineous parents (cousins I°) of Turkish Origin. II.1: *CSDE1* patient (index), II.2: 16-year-old healthy brother II.3: 19-year-old healthy brother. (b) I.-III.: Brain MRI at the age of 3: mildly reduced brain volume with moderate dilation of the ventricular system, slight enlargement of prefrontal subarachnoid space, slim white matter, and a thin and short corpus callosum with a partial lack of the splenium. I. T1 transversal, II. T2 transversal, III. T1 sagittal, IV.-VI.: Brain MRI at the age of nine: Signs of a mildly reduced brain volume, but some further development to normality with a slight decrease of the ventricular dilation and a normalization of the size of the prefrontal subarachnoid space. The corpus callosum remains thin and short with a partial lack of the splenium. IV. T1 transversal, V. T2 transversal, VI. T1 sagittal. (c) Photographs of our *CSDE1* patient at the age of 8 years and 6 months, I. from front, II. from side, and III. from behind. The patient started crying with joy when asked about her watch, only to cry again because of anxiety due to the examination and cried throughout the whole examination, unable to stop. Note the hypotonia of the trunk, plantigrade footrest, internal rotation, and deviating foot axis of the left foot

evaluations and basic metabolic work-up (plasma and cerebrospinal fluid) showed no abnormalities.

3.4 | 3–5 years of age (preschooler)

Motor and speech development remained delayed, but continuous developmental progress was noted by the parents. Independent walking was achieved at 3 years and 10 months, she was still only able to speak some single words, but speech comprehension improved. Clinical examination showed no dysmorphisms, the patient was shy but friendly, did not speak with the examiner. Her gait was broad based and a bit unsteady. Under suspicion of a neuropathy, nerve conduction velocities were performed with normal results. Mild ataxia was seen when reaching for objects. To exclude ataxia telangiectasia alpha-fetoprotein was measured and showed a normal result. Getting up from supine to sitting and getting up from floor was not possible, respectively.

At the age of 3 years and 11 months, a testing via Bayley-Scales of Infant Development II (Bayley II) was performed (Snijders Oomen non-verbal intelligence test [SON-R] and Kaufman Assessment Battery for Children [K-ABC] not being possible to be performed due to the neurodevelopmental delay) revealing a delay of 2 years (cognitive-verbal developmental age: 22 months).

At the age of 4 years 8 months, parents reported further developmental progress, meaning her gait being a bit more stable. They reported problems climbing stairs and getting up from floor. At this age, she was able to speak a maximum of 20 words in single-word-sentences. Clinical examination showed no further evidence for ataxia. Performance of an array-based CGH showed a normal result, with additionally reported large homozygous regions.

At the age of 5 years and 11 months, parents reported a persistent lack of independence in eating/drinking, toileting, and dressing. The patient was now able to get up from supine to sitting without help but needed still support to get up from floor. She was shy but friendly and able to understand simple commands of the examiner and put them into practice. Patellar tendon reflexes were vivid with enlarged reflex zones.

3.5 | 6–10 years of age (school-aged child)

At the age of 6 years and 11 months, the SON-R intelligence test was possible to be performed and showed an intelligence quotient of 50 (normal range 85–115), with scale of action 50 and scale of thought 50. Additionally, the general scale of speech of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) was done and showed a result of 45 (normal range 85–115). Parents reported slight motor progress, now being able to walk 30 min and learning to crawl. She was still not able to get up from floor, neither to sit down all by herself. She was only able to climb stairs by herself but not to descend; in this case, she needed to be carried by her parents. She was still dependent on her parents in all tasks concerning daily life. Clinical examination revealed a truncal muscle hypotonia and finger tapping was mildly ataxic.

At the age of 8 years and 3 months, the parents did not report further developmental progress, but they mentioned her being interested in toys and loving to play with her dolls. She was going to a special school with focus on mental development and made friends there. At this examination, she did not cooperate very well, was very shy and started crying immediately. The patient was still not able to get up and sit down all by herself. An intermittent action tremor was observed, the gait was abnormal with plantigrade footrest, internal rotation of the left foot, spindly with broad base. Additionally, clonus of both feet (right > left) and muscular hypotonia of the trunk were notable. Deep tendon reflexes were laterally identical, vividly triggerable. Electrophysiological studies were not performed.

At the age of 8 years and 6 months, parents reported additional features concerning her emotional state. They described her as a very anxious child, having frequently changing moods, crying very often as reaction to anxiety as well as to happiness. This was confirmed during the clinical examination (Figure 1c I–III), where she started crying with joy when asked about her watch, only to cry again because of anxiety due to the examination. She cried throughout the whole examination, unable to stop. Due to the new symptoms (intention tremor, clonus, abnormal gait, and mood changes) additional diagnostic work-up was performed. Brain MRI was repeated, showing some further development to normality with a slight decrease of the ventricular dilation and a normalization of the size of the prefrontal subarachnoid space. The corpus callosum, however, remained thin and short with a partial lack of the splenium and there were still signs of a mildly reduced brain volume (Figure 1b IV–VI). MRI of the spinal cord was complemented, showing normal results. Additionally, trio exome sequencing was initiated.

At her last appointment, the patient was 10 years and 4 months old. She was finally able to get up all by herself. In the meantime, she had been fitted with foot orthoses to improve her gait and a wheelchair due to exercise intolerance. She was still only able to speak a few words with her parents, verbal communication with the examiner was not possible. She vacillated between anxiety and laughter. The body measurements were within the normal range (weight 43.5 kg [85. percentile], height 138.6 cm [25. percentile], body mass index 22.6 kg/m^2 [95. percentile] (percentiles from: Kromeyer-Hauschild et al., 2001), head circumference 51.5 cm [15. percentile] (percentiles from: Braegger et al., 2011). She still showed truncal hypotonia and abnormal gait with hardly any rolling movement of the left foot, due to reduced range of motion of left upper ankle and foot deformity (bending foot on the right, hollow and sickle foot on the left) causing significantly increased load on the outer foot edges and internal rotation of the left foot. Clonus was still present in her right upper ankle join. Lifting the head from a lying position was possible, getting up from the floor was done cumbersome, first via the side and then via the four-footed stand, finally pulling herself up with the help of the examination bench.

4 | RESULTS

Regular karyotyping (46, XX) and array based CGH were normal, the second revealing additionally reported large homozygous regions. Trio exome sequencing showed a heterozygous de novo nonsense variant in the *CSDE1* gene (HGNC: 29905): c.367C>T; p.R123*, ENST00000369530. This high effect impact is expected to result in absent protein due to the premature stop gain and annotated as disease causing by Mutation Taster but displays a CADD score of 36. This change is absent from all the control populations (1000 genomes project and GnomAD database; http://gnomad.broadinstitute.org/). The chromosomal position based on hg38 coordinates is: chr1:114738043 G>A.

A search for homozygous variants across the whole exome of this patient retrieves a total of 12 variants. Of these, three genes (*ARMC4*, *CEP290*, and *CA5A*) are associated with human disease, yet none of them explains the phenotype of the patient.

5 | DISCUSSION

Here, we report on the development of the neuropediatric phenotype in a girl carrying a de novo p.R123* nonsense variant in *CSDE1*. Given that this pathogenic variant was already reported three times in literature, one might speculate that it represents a recurrent—so far even the most frequent—variant associated with the *CSDE1*-related phenotype. The addition of our case might suggest that this is a mutational hotspot.

Interestingly, Guo and colleagues describe in total 18 patients with *CSDE1* variants, of whom eight are *de novo*, eight inherited (five paternally and three maternally) and two with undetermined inheritance. This finding is most likely explained by incomplete penetrance. The p.R123* variant was *de novo* twice and maternally inherited once (Guo et al., 2019). The fact that the nonsense variant is *de novo* in our patient in combination with the fitting phenotype, suggests a pathogenicity of this particular variant in a dominant pattern. Nevertheless, longitudinal studies of *CSDE1* families, including more detailed phenotypic and genetic assessment of carriers, are needed to better understand the progression and risk factors associated with variable expression of this disorder.

The clinical longitudinal study of our patient revealed some concordance in the core features (neurodevelopmental delay and ID) previously described by Guo and colleagues about 18 patients with likely disease-causing variants in *CSDE1*. In their report, neurodevelopmental delay and intellectual disability were found in 17 out of 17 patients and autism was observed in 11 out of 17 patients (Guo et al., 2019) but was in contrast, not diagnosed in our patient. However, she showed some accompanying psychological symptoms often associated with autism, like increased anxiety (7/17 patients reported by Guo and colleagues) (Guo et al., 2019), peculiarities in the perception and processing of environmental and sensory stimuli, getting her into situations of sensory overload resulting in pathological laughter and crying. Further symptoms reported by Guo and colleagues (Guo et al., 2019) like epilepsy/EEG abnormalities, macrocephaly, sleep disturbances, behavioral problems (repetitive, obsessive, self-injurious or aggressive behavior/attention deficit hyperactivity disorder), eye abnormalities, recurrent infections, hand deformity, and short stature were not present in our patient.

Our patient showed additional neurological symptoms expanding the phenotype associated with *CSDE1* by adding signs of muscle weakness (not able to get up from floor until the age of 9 years and exercise intolerance), increased tone at the upper ankle joints and clonus (pyramid track sign), abnormal gait (gait instability requiring foot orthoses), and intention tremor (cerebellar sign). A similar severity of motor delay was reported very recently by El Khouri and colleagues, who described a patient with a nearby located *CSDE1* variant (c.362C>A; p.S121*), who was not able to walk independently until the age of 8, showed an ataxic gait thereafter, as well as additionally pronounced facial dysmorphisms, repetitive behavior associated with severe ID and absence of speech but normal MRI of the brain (El Khouri et al., 2021).

MRI of the brain (performed twice) of our patient showed mildly reduced brain volume with moderate dilation of the ventricular system, slight enlargement of prefrontal subarachnoid space, slim white matter and a thin and short corpus callosum with a partial lack of the splenium. This is consistent with the findings of Guo and colleagues, who reported in 7 out of 17 patients abnormalities on brain MRI, for example, prominent ventricular system in five patients, thin corpus callosum in two patients, vermis hypoplasia in two patients and white matter alterations in one patient. Interestingly, the two patients with thin corpus callosum were not the ones with the same variant (Table 1), which suggests that this is not a variant-specific abnormality, but is generally attributable to mutations in *CSDE1* as well as in autism in general (Wegiel et al., 2017). Hence, a comparison of our patient with the three *CSDE1* patients reported by Guo and colleagues (all carrying the same variant: c.367C>T; p.R123*) did reveal some similarities but no general consistency (Table 1). ID as well as speech and motor delay were present in all patients, but this fact is probably more attributable to the frequency of the symptoms present in *CSDE1* in general. In contrast, autism was only present in one patient with the R123* variant, but in 11 out of 17 patients reported by Guo and colleagues. Hypotonia and anxiety were each present in three of the four patients with the R123* variant, some of the other symptoms in two out of four patients, what makes interpretation difficult. In summary, more cases would be helpful for further deduction.

Muscle weakness as an explicit clinical symptom has not been reported for *CSDE1* patients previously. However, a possible explanation might be that this clinical finding was mistaken under a hypotonia diagnosis, which is already included in the phenotypic spectrum of *CSDE1* probands. The possibility of an involvement of *CSDE1* in muscle function is supported by the expression of *CSDE1* in muscle tissue (Figure 2) but needs certainly further evaluation in the future using muscle biopsies from *CSDE1* patients (if available), as well as muscular phenotyping of the above-mentioned animal models and assessment of potential muscle weakness in further *CSDE1*-patients in larger studies. Along this line, as long as these

TABLE 1 Comparison of our patient with the three *CSDE1* patients reported by Guo and colleagues, all carrying the same variant: c.367C>T; p.R123*

Category				
Region	Simons Simplex Collection	California, USA	Adelaide, Australia	Germany, Essen
Country/ethnicity information	Caucasian	European/Middle-Eastern	European	Turkey
CSDE1 variant (NM_001242891)	c.367C>T; p.R123*	c.367C>T; p.R123*	c.367C>T; p.R123*	c.367C>T; p.R123*
Mutation detection method(s)	WES/MIPs	WES	MIPs	trio WES
Mutation inheritance	de novo	de novo	Maternal	de novo
Age at last examination (years)	17	7	19	10
Sex	Female	Male	Male	Female
Neonatal				
Delivery—weeks' gestation	40	38–39	Full term	38
Delivery—mode	Vaginal	Caesarean section	Unknown	Vaginal
Birth weight (percentile and/or SD)	3600 g	3230 g	3400 g	3790 g (93th percentile)
Birth length (percentile and/or SD)	na	51 cm	51 cm	50 cm (43th percentile)
Birth OFC (percentile and/or SD)	na	unknown	35 cm (98th percentile)	35 cm (71th percentile)
Infant feeding difficulties	na	Yes	Yes	Yes, problems chewing and swallowing small pieces of food at 2 years
Failure to thrive	na	No	No	No
Neurodevelopmental problems				
Autism/autistic features	Yes	No	No	No
Intellectual disability	Yes	Yes	Yes	Yes
Intellectual quotient (method, score)	WISC at 17 years: IQ 42	Learning disability	Unknown	WPPS at 7 years: IQ 45
Childhood speech delay	Yes	Initially delayed, had speech therapy, at 2.5 years words, phrases	Yes	Yes, profound (at 10 years only single word sentences)
Childhood motor delay	Yes	Yes	Yes	Yes, profound
Regression of developmental milestones	Word loss	Unknown	na	No
Behavior problem				
Anxiety (type)	Yes	Possible, difficult transitioning, sensor integration	No	Yes, profound (frequently changing moods, crying very often as reaction to anxiety as well as to happiness)
ADHD (criteria)	Yes	Yes, receiving medication	No	No
Repetitive behavior	Yes	No	Yes	No
Obsessive–compulsive behavior	No	No	Yes	No
Aggressive behavior	No	No	No	No
Self-injurious behavior	Unknown	No	No	No
Bipolar disorder	Unknown	Unknown	Unknown	No

TABLE 1 (Continued)

Schizophrenia	Unknown	Unknown	Episode of psychosis, receiving medication	No
Neurological problems				
Muscle weakness	Unknown	Walked with 16 months, pedaling with 7 years, difficulty holding heavy things, gets "tired," holds pencil differently, can swim	Unknown	Walked with 3 years 10 months, problems climbing stairs, able to get from supine to sitting with 5 years 11 months and up from floor with 10 years
Muscle hypotonia	Yes	No	Yes	Yes, predominantly truncal hypotonia
Macrocephaly	Yes	No	Yes	No
Microcephaly	Yes	Yes	Yes	Yes
MRI Brain abnormalities	No	Asymmetry of lateral ventricles, associated with sulci with apparently thickened cortex right parieto-occipital junction, possible cortical dysplasia	No	Mildly reduced brain volume with moderate dilation of the ventricular system, slight enlargement of prefrontal subarachnoid space, slim white matter and a thin and short corpus callosum with a partial lack of the splenium
EEG abnormalities	Abnormal	Normal at 2 years	Abnormal	Normal
Seizure (specify type, relation with fever, frequency, etc.)	No	No	Yes	No
Sleep disturbances	Yes	Not yet dry at night	No	No
Systemic				
Weight (percentile and/or SD)	93.4 kg	19.1 kg (7th percentile) at 7.25 years	75th to 90th percentile	43.5 kg (85th percentile) at 10.3 years
Height (percentile and/or SD)	161.5 cm	100.8 cm (<1st percentile) at 7.25 years	25th to 50th percentile	138.6 cm (25th percentile) at 10.3 years
Head circumference (percentile and/or SD)	59 cm (+3.19SD)	53 cm (77th percentile) at 7.25 years	>98th percentile	51.5 cm (15th percentile) at 10.3 years
Gastrointestinal disturbance	Chronic, primary constipation (onset at age 3 years) with intermittent bloating	No	No	No
Short stature	No	Yes	No	No
Hand deformity	Polydactyly	No brachydactyly, some clinodactyly	No	No

Abbreviations: MIPs, molecular inversion probes; na, not applicable; WES, whole exome sequencing; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; SD, standard deviation.
Source: Table adapted from Guo et al. (2019).

studies are not available, such clinical (even single case) reports are important for the diagnosing and treating physicians. Nevertheless, the muscle weakness could also be a consequence of the pyramidal tract signs and cerebellar symptoms and thus be of neuronal origin. If this would be the case, one might speculate that one functional *CSDE1* copy is sufficient to maintain muscle function by providing critical protein level. On a general note, there is a fundamental lack of data on muscle function in patients with syndromic diseases, who in almost all cases, show pronounced muscle hypotonia and often also signs of mild muscle weakness and/or exercise intolerance. Due to neuromuscular symptoms, these patients may primarily present at neuromuscular clinics and finding the genetic diagnosis may be hampered by suing NGS panels including only genes involved in neuromuscular diseases.

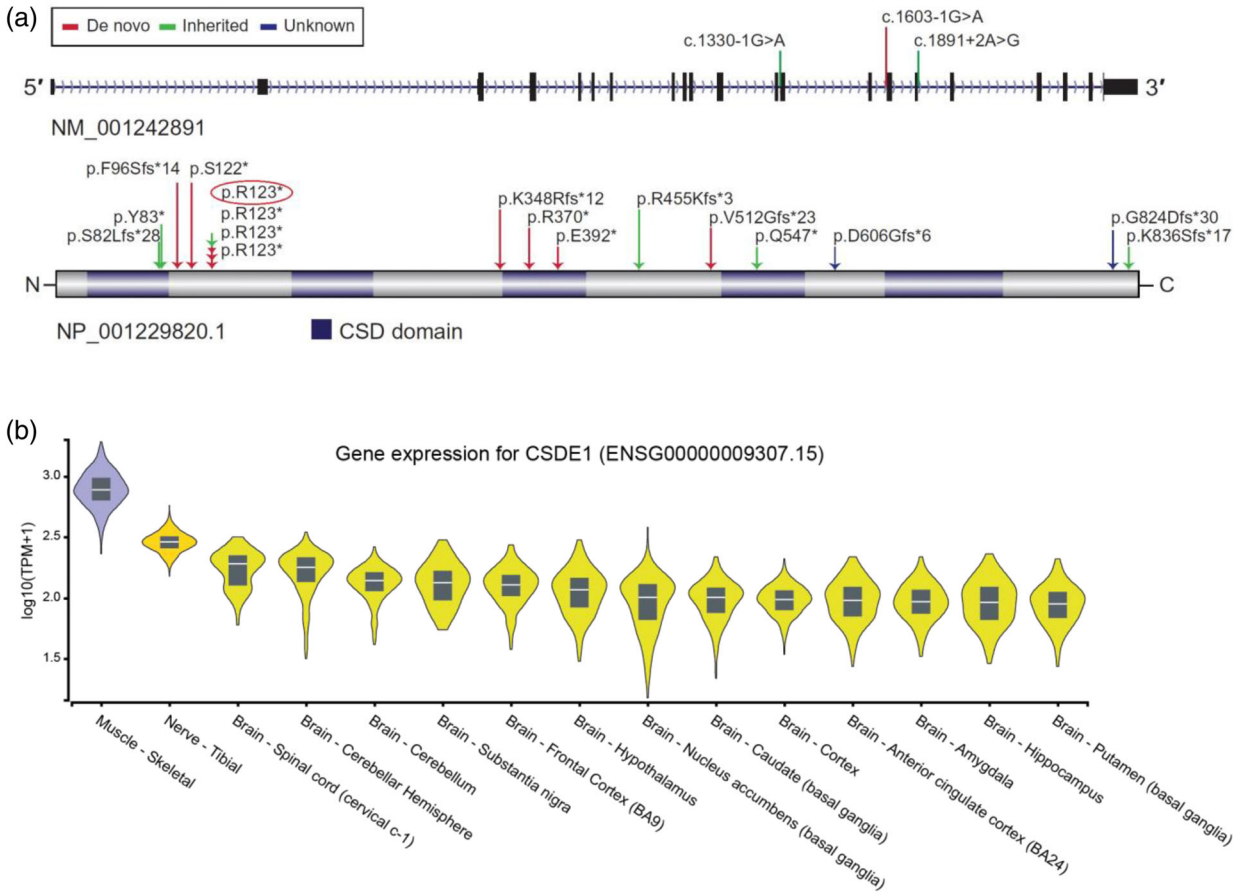


FIGURE 2 (a) Diagram of the canonical *CSDE1* isoform (NM_001242891.1 and NP_001229820.1). The locations of the variants reported until today are indicated. Circled in red = our patient, CSD = Cold-shock domain. *Source*: Figure adapted from Guo et al. (2019). (b) GTEx-based in silico analysis of tissue expression of *CSDE1*. Expressed are log10-ratios of transcripts per million (TPM) in the respective tissues/nervous areas as violine plots

In addition, our report shows that even if the parents of (neurological) patients are consanguineous (large homozygous regions reported in array-based CGH), dominant de novo variants might still be causative for the manifestation of the underlying phenotype (Monies et al., 2019) and should therefore be considered in the interpretation of exome datasets.

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CONFLICT OF INTEREST

The authors report no disclosures relevant to the manuscript.

AUTHOR CONTRIBUTIONS

Andrea Gangfuß conceptualized and designed the study, drafted together with Andreas Roos and Heike Kölbel the first version of the manuscript, interpreted results and was principally responsible for the final content. Ulrike Schara-Schmid reviewed and revised the manuscript for important intellectual content. Bernd Schweiger, Hanns Lochmüller, Rita Horvath, and Ana Töpf analyzed data and interpreted results. All authors contributed to the final manuscript and agreed to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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